General

Guideline Title

American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome.

Bibliographic Source(s)

Rubenstein JH, Enns R, Heidelbaugh J, Barkun A, Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome. Gastroenterology. 2015 Sep;149(3):777-82. [7 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the quality of evidence (high, moderate, low, very low) and strength of recommendation (strong, weak) are provided at the end of the "Major Recommendations" field.

Recommendations

- In patients without a personal history of colorectal or another cancer but with a family history suggestive of Lynch syndrome, the American Gastroenterological Association (AGA) suggests that risk prediction models be offered rather than doing nothing. (Conditional recommendation, Very low quality of evidence)
- In patients without a personal history of colorectal or another cancer but with a family history suggestive of Lynch syndrome, the AGA suggests that risk prediction models be offered rather than proceeding directly with germline genetic testing. (Conditional recommendation, Very low quality of evidence)
- The AGA recommends testing the tumors of all patients with colorectal cancer with either immunohistochemistry (IHC) or for micro satellite instability (MSI) to identify potential cases of Lynch syndrome versus doing no testing for Lynch syndrome. (Strong recommendation, Moderate quality of evidence)
- The AGA suggests that in patients with colorectal cancer with IHC absent for *MLH1*, second-stage tumor testing for a *BRAF* mutation or for hypermethylation of the *MLH1* promoter should be performed rather than proceeding directly to germline genetic testing. (Conditional recommendation, Very low quality of evidence)
- The AGA recommends surveillance colonoscopy (versus doing nothing) in persons with Lynch syndrome. (Strong recommendation, Moderate quality of evidence)

- The AGA suggests that surveillance colonoscopy should be performed every 1 to 2 years versus less frequent intervals. (Conditional recommendation, Low quality of evidence)
- The AGA suggests that aspirin be offered for cancer prevention in patients with Lynch syndrome. (Conditional recommendation, Low quality of evidence)

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories of Quality of Evidence

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect might be substantially different from the estimate of the effect.
Very Low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

GRADE Strength of Recommendations

	For the Patient	For the Clinician
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Weak/Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids might well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

Clinical Algorithm(s)

An algorithm titled "Diagnosis and Management of Lynch Syndrome: Clinical Decision Support Tool" is provided in the original guideline document.

Scope

Disease/Condition(s)

Lynch syndrome (previously referred to as hereditary nonpolyposis colorectal cancer syndrome)

Guideline Category

Diagnosis

Management

Clinical Specialty

Gastroenterology

Intended Users

Physicians

Guideline Objective(s)

To aid in identifying cases of Lynch syndrome and management of risk of colorectal cancer

Target Population

- Adults without a personal history of colorectal cancer or another cancer but with a family history of cancer that could be suggestive of Lynch syndrome
- Adults with colorectal cancer
- Adults with Lynch syndrome

Interventions and Practices Considered

1. Risk prediction models (patients without a personal history of colorectal or another cancer but with a family history suggestive of Lynch syndrome)
2. Testing tumors of all patients with colorectal cancer with either immunohistochemistry (IHC) or for microsatellite instability (MSI)
3. Second-stage tumor testing for a *BRAF* mutation or for hypermethylation of the *MLH1* promoter (patients with colorectal cancer with IHC absent for *MLH1*)
4. Surveillance colonoscopy
5. Aspirin

Major Outcomes Considered

- Test performance characteristics of diagnostic tests, including
  - Sensitivity and specificity
  - Psychological distress
- Quality of life
- Incidence and prevalence rates of colorectal cancer
- Costs

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search Strategy

An experienced librarian conducted 3 distinct computerized medical literature searches (according to grouping of population, intervention, comparator, and outcome [PICO] questions using a similar search strategy) using the following databases from inception to November 18, 2013: MEDLINE, EMBASE, Cochrane, and Health Technology Assessment.

All searches included a highly sensitive search strategy to identify reports of randomized trials, cohort studies, or case-control studies using a combination of controlled vocabulary and text words. The first search related to PICO questions 1, 2, 4, and 5 included the following terms: (1) hereditary nonpolyposis colorectal cancer or Lynch and (2) colonoscopy or immunohistochemistry or genetic testing or microsatellite instability or acetylsalicylic acid (complete search strings are shown in Appendix 2 of the technical review [see the "Availability of Companion Documents" field]). The search related to PICO question 3 addressed the following: (1) colorectal neoplasms and (2) *BRAF* mutation or *MLH1* DNA methylation (see Appendix 3 in the technical review). In addition, recursive searches and cross-referencing was performed; hand searches of articles identified after the initial search were also completed. The PICO questions can be found in Appendix Table 1 of the technical review.

Trial Selection and Patient Population

All fully randomized controlled trials or observational studies published in English were included. Studies comprising pediatric populations as well as letters, notes, case reports, or comments were excluded.

Number of Source Documents

Studies involved in the review and meta-analysis:

- Population, intervention, comparator, and outcome (PICO) question 1: 16 studies
- PICO question 2: 41 studies
- PICO question 3: 25 studies
- PICO question 4: 5 studies
- PICO question 5: 2 studies

See the PRISMA flow diagrams and Quality Assessment of Diagnostic Accuracy Studies (QUADAS) assessments for each PICO question in Appendix Figures 1-5 in the technical review (see the "Availability of Companion Documents" field) for further information on the results of the literature search.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories of Quality of Evidence

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect might be substantially different from the estimate of the effect.
Very Low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Validity Assessment

Study eligibility was assessed independently by 3 investigators, with discrepancies resolved after discussion and reaching a consensus. Data extraction was thoroughly performed by content experts. Risk of bias for individual studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool for observational diagnostic studies, a modified Jadad score (one point added if allocation was concealed) for randomized trials, and the Newcastle–Ottawa Scale for observational studies. The quality of the evidence for each statement was rated as very low, low, moderate, and high based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Appendix 5 in the technical review [see the "Availability of Companion Documents" field]); disagreements were resolved by discussion. See the "Rating Scheme for the Strength of the Evidence" field for the quality of evidence definitions.

Statistical Analysis

Study data were carefully extracted in 2x2 tables for intervention-related outcomes and comparators. Sensitivity and specificity were calculated and reported as proportions and 95% confidence intervals (CIs). Pooled estimates determined with meta-analysis using a bivariate linear mixed model were calculated by including all studies that provided data allowing computation of both sensitivity and specificity. Heterogeneity is to be expected in the results; therefore, the investigators used random effects models. To give an indication of the between-study heterogeneity, summary receiver operating characteristic curves were generated, including sensitivity and specificity confidence regions for the summary points as well as the prediction region. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC) and Review Manager (RevMan) version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2008).

Methods Used to Formulate the Recommendations

Expert Consensus

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

This guideline was developed by the American Gastroenterological Association (AGA) Clinical Guidelines Committee and approved by the AGA Governing Board.

The guideline was developed using the AGA Process for Developing Guidelines (see the "Availability of Companion Documents" field). Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and best practices as outlined by the Institute of Medicine. GRADE methodology was used to prepare the accompanying technical review on focused questions and their related specific population, intervention, comparison, and outcome (PICO). Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The quality of available evidence on each question was first judged by the technical review panel of content and methodological experts according to the published GRADE process (see the "Rating Scheme for the Strength of the Evidence" field). Reasons justifying grading are detailed in the guideline text when appropriate. The guideline authors met with the technical review panel and a patient representative to discuss the evidence. The guideline authors subsequently met privately and drafted recommendations, taking into account the quality of evidence, as well as the balance between benefits and harms, patient preferences, and resource utilization. Such pertinent considerations are also detailed in the guideline text when relevant. The strengths of the recommendations were categorized as (1) strong, (2) weak/conditional, or (3) no recommendation according to GRADE terminology (see the "Rating Scheme for the Strength of the Recommendations" field).

Formulation of Clinical Questions

The participants were selected by the AGA Clinical Guidelines Committee based on clinical content and guidelines methodological expertise. Focused questions were generated, and a statement was framed for each question in terms of PICO. In accordance with a modified Delphi method, the questions and PICO statements were developed by multiple structured iterations until a consensus among experts was reached. The final proposed clinically pertinent, focused questions and PICO statements related to 3 different populations: adults without a personal history of colorectal cancer or another cancer but with a family history of cancer that could be suggestive of Lynch syndrome, adults with colorectal cancer, and adults with Lynch syndrome. The final set of questions and statements was approved by the AGA Governing Board. The final PICO questions are shown in Appendix Table 1 of the technical review (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Strength of Recommendations

	For the Patient	For the Clinician
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Weak/Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids might well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

Cost Analysis

- A cost-effectiveness analysis has suggested that a threshold of greater than 5% predicted probability of carrying a Lynch syndrome mutation should prompt germline genetic testing if universally applied to 25-year-old patients. However, the threshold could be lower in middle-aged adults and as the cost of genetic testing decreases. If the probability is above the threshold, then germline genetic testing for mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* should be offered.
- A cost-effectiveness model estimating life expectancy and health care costs of frequent colonoscopy surveillance versus no surveillance determined that surveillance of people who are gene carriers for Lynch syndrome increased life expectancy by 7 years and costs of surveillance were less than costs of no surveillance for colorectal cancer.

Also refer to the "Cost-effectiveness" sections of the technical review (see the "Availability of Companion Documents" field).

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

This document presents the official recommendations of the American Gastroenterological Association Institute on the diagnosis and management of Lynch syndrome. This guideline was developed by the American Gastroenterological Association (AGA) Clinical Guidelines Committee and approved by the AGA Governing Board.

The draft recommendations were combined into a clinical decision support tool and then opened to public comment, edited, and approved by the Governing Board of the AGA.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of patients with Lynch syndrome

Potential Harms

- In one high-quality randomized controlled trial the adverse risks of aspirin therapy (1% risk of gastrointestinal bleeding and <1% risk of stroke greater than placebo) were not statistically significant. The recommended dose and frequency of aspirin to offer patients with Lynch syndrome for cancer prevention is unknown. An individualized approach is best, considering the patient's personal risk of adverse events with aspirin therapy. The recommended dose and frequency of aspirin to offer patients with Lynch syndrome for cancer prevention is unknown. Moreover, the dose tested in this trial was high and uncertainties about risks versus benefits remain, so an individualized approach is best, considering the patient's personal risk of adverse events with aspirin therapy.
- Because immunohistochemistry (IHC) and microsatellite instability (MSI) testing have comparable sensitivities and specificities, their implementation has varied depending on the level of expertise and availability within a given institution. Although many sites can technically perform IHC, the results must be interpreted with caution; appropriate training and experience of pathologists is required to ensure that they are adept at interpreting the data. Furthermore, a system for systematic follow-up of all positive results must be in place.
- The meta-analysis in the technical review (see the "Availability of Companion Documents" field) found that *BRAF* mutations and hypermethylation of the *MLH1* promoter are also found in some patients with Lynch syndrome. Therefore, using second-step testing may in fact result in some small proportion of cases of Lynch syndrome being missed (no more than 10%, but likely substantially fewer than that).

Qualifying Statements

Qualifying Statements

Although most of the recommendations are conditional, this should not be confused with making no recommendation. Instead, based on the available evidence, the American Gastroenterological Association (AGA) is able to make recommendations in those scenarios for the current management of patients, but the recommendation could conceivably change in the future in the face of new evidence. Given the large incidence of colorectal cancer, one recommendation in particular may be ripe for consideration as a process measure of quality of care: tumor testing in newly diagnosed cases of colorectal cancer to identify cases of Lynch syndrome.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Patient Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Rubenstein JH, Enns R, Heidelbaugh J, Barkun A, Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome. Gastroenterology. 2015 Sep;149(3):777-82. [7 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Sep

Guideline Developer(s)

American Gastroenterological Association Institute - Medical Specialty Society

Source(s) of Funding

American Gastroenterological Association Institute

Guideline Committee

American Gastroenterological Association Institute Clinical Practice Guideline Committee

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Financial Disclosures/Conflicts of Interest

All members were required to complete disclosure statements. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and none of the disclosures were potentially related to the content of this guideline.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Gastroenterology Journal Web site.

Availability of Companion Documents

The following are available:

- American Gastroenterological Association technical review on the diagnosis and management of Lynch syndrome. Gastroenterology. 2015 Sep;149(3):783–813.e20. Available from the Gastroenterology Journal Web site.
- The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol. 2013 Apr;11(4):329-32. Available from the Clinical Gastroenterology and Hepatology Web site.
- AGA process for developing guidelines. 2014 Dec. Available from the American Gastroenterological Association (AGA) Web site.

This guideline also has an accompanying continuing medical education (CME) activity available from the Gastroenterology Journal Web site.

Patient Resources

The following are available:

- Lynch syndrome: AGA patient guideline summary. Gastroenterology. 2015 Sep;149(3):814-5. Available from the Gastroenterology Journal Web site.
- A patient guide: understanding Lynch syndrome. 2015 Sep. Available from the American Gastroenterological Association (AGA) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors

or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on February 2, 2016. The information was verified by the guideline developer on February 29, 2016.

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